REMARKS

Entry of the amendment and reconsideration of the application are respectfully requested. Claims 1-3, 5-8, 11, 25, 26, 29, 31-34, 37, 39, and 40 are pending in the application. Claims 1-8 [sic], 11, 12 [sic], 25, 26, 29-34 [sic], and 37-40 [sic] have been rejected under 35 U.S.C. § 103(a) over various cited documents.

I. Amendments

Claim 3 has been amended to recite a method for producing a human cell line for use in producing one or more cytokines. Such an amendment is fully supported in the application, including by originally filed claim 3.

II. Rejections under 35 U.S.C. §103(a)

Claims 1-8 [sic], 11, 12 [sic], 25, 26, 29-34 [sic], and 37-40 [sic] stand rejected under 35 U.S.C. § 103(a) as allegedly obvious by Dixit (U.S. Patent No. 6,015,665); Lau. (U.S. Patent No. 6,159,712) and Suzuki et al. (Derwent Abstract XP-002170158 and machine translation of Japanese patent application JP9-163983). This rejection is respectfully traversed for the following reasons.

Applicants would first like to clarify that claims 12, 30, 38 were canceled in the amendment submitted July 28, 2003 and claim 4 was cancelled in the amendment submitted April 21, 2004. The listing of claims in the paragraph above, should properly read 1-3, 5-8, 11, 25, 26, 29, 31-34, 37, 39, and 40.

A. Summary of Present Invention

The present invention, as set forth in claim 1, relates to a human cell composition for use in producing one or more cytokines. The cell line is characterized by expression of the coding sequence for an anti-apoptotic protein and a level of cytokine production that is at least two times (2X) the level of cytokine production exhibited by a corresponding parental cell line that does not express the coding sequence for the anti-apoptotic protein.

The present invention, as set forth in amended claim 3, relates to a method of producing a human cell line for use in producing one or more cytokines. The method includes:

(i) obtaining a parental human cell line capable of producing one or more cytokines;

(ii) modifying the cells by introducing an expression vector comprising the coding sequence for CrmA operably linked to a first promoter, and additional control elements necessary for expression in human cells, into the cells of said cell line;

(iii) screening and selecting for CrmA-expressing cells; and

(iv) treating the CrmA-expressing cells in a manner effective to result in enhanced cytokine production, wherein the modified and treated cell line is characterized by a level of cytokine production that is at least two times (2X) the level of cytokine production by the corresponding not-modified parental cell line.

B. The Cited Documents

Dixit describes a method for preventing or inhibiting apoptosis in a cell. The method includes introducing into the cell a nucleic acid coding for CrmA or for a gene product having CrmA activity. The invention is described in column 1, lines 57-63, as satisfying the need to maintain T cell function and viability in HIV infected individuals and to provide systems to screen for new drugs that may assist in maintaining the cellular immune response. Dixit is therefore concerned with preventing lymphocyte death and maintaining T cell viability in patients infected with HIV (See also column 9, lines 23-42).

Lau describe a method to increase production of interferon in a cell by modifying the cell to overproduce dsRNA dependent kinase (DSRNA-PKR or PKR).

Suzuki et al. describe a method of improving production of a useful target material, such as an antibody, a cytokine, etc., from a cell by inhibiting apoptosis of the cell. Apoptosis is inhibited by introducing into the cell an apoptosis inhibitor gene, such as CrmA, Bcl-2, BAG-1, etc.

C. Analysis

According to M.P.E.P. § 2143, three basic criteria must be met to establish a case of obviousness. "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2143.

It is Applicants' position that the first criterion required to establish a case of obviousness has not been met. Specifically, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings.

Whether there would be a high expectation of success in combining the references, e.g., using the cell line of Dixit for the production of useful matter, such as a cytokine, given the teaching of Suzuki et al., is not the appropriate standard. There must be some teaching or suggestion to combine the teaching of Dixit with the teaching of Suzuki et al. and no such teaching or suggestion exists. Moreover, one skilled in the art would not be motivated to make such a combination as such a combination would be contrary to the express purpose of the teachings of Dixit.

Dixit is relied on for teaching the transformation of MCF-7 and BJAB cells (human-derived cells) with a vector encoding CrmA. Suzuki et al. is relied on for teaching increasing the ability of a cell to produce useful matter (product), such as cytokines, by preventing apoptosis from killing the cell prematurely. Suzuki et al. is further relied on for teaching increased cell life translates into an increased production of the product (citing paragraph 021) and also for teaching use of a cell line to which an apoptosis gene has been introduced, such as CrmA. The Examiner concludes it would have been obvious to utilize the cell line taught by Dixit for the production of useful matter, such as a cytokine, as allegedly taught by Suzuki et al. and that one skilled in the art would have a high expectation of success in using the cell line of Dixit for the production of useful matter, such as a cytokine, given the teaching of Suzuki et al.

As mentioned above, Dixit describes a method for preventing or inhibiting apoptosis in a cell by introducing into the cell a nucleic acid coding for CrmA or for a gene product having CrmA activity. Dixit is concerned with preventing lymphocyte death and maintaining T cell viability in patients infected with HIV (See also column 9, lines 23-42). Conversely, the present invention as recited in claim 1 relates to a human cell line characterized by expression of the coding sequence or an anti-apoptotic protein

and having an enhanced level of cytokine production that is at least two times the level of cytokine production exhibited by a corresponding parental cell line. The invention recited in claim 3 relates to a method of producing such a human cell line. As the Examiner has previously noted, cytokine production is well documented as inducing apoptosis. For example, as noted in the specification, and supported in the scientific literature, cells having an enhanced level of some cytokines alone or in combination are often apoptotic, possibly due to up-regulation of the Fas receptor. (See, for example, previously sent abstracts of Yasuoka, Y. et al., Exp. Cell Res., 271(2):214 (2001) finding that combination of TNFα and IFNα induce apoptotic cell death; Shin, E.C., *et al., Int. J. Cancer*, 93(2):262 (2001) reporting that IFNγ induces cell death via apoptosis; Lafleur, E.A., *et al., Cancer Res.*, 61(10):4066 (2001) reporting that IL-12 up-regulates Fas expression leading to apoptosis; See previously sent papers of Ling, Z. *et al., Diabetes*, 52:2497 (2003) finding that IL-1β and TNFα exert distinct apoptotic effect; Chung, I., *et al., Blood*, 101:1324 (2003) reporting that IFNγ upregulates Fas receptor leading to apoptosis; See specification page 4, lines 35-39 reporting that expression of PKR, which enhances cytokine production, triggers apoptosis and cites of Yeung, M.C., *et al., Proc Natl Acad Sci USA* 93:12451-12455 (1996) and Donze, O., *et al., Virol* 256:322-329 (1999) previously submitted with Form 1449 IDS.)

Because Dixit is concerned with preventing or inhibiting apoptosis in order to prevent lymphocyte death and maintain T cell viability in patients infected with HIV and cytokine production induces apoptosis, there is absolutely no motivation to combine this teaching of Dixit with Suzuki et al. to enhance cytokine production the cell line of Dixit because this would be inconsistent with preventing lymphocyte death and maintaining T cell viability. Therefore, to modify the teaching of Dixit to include the idea of enhancing cytokine production is contrary to the express purpose of Dixit of inhibiting or preventing apoptosis.

Lau is relied on for teaching a method of producing a cell that is able to overexpress cytokines wherein the cell comprises a vector containing PKR and cytokine expression is stimulated by induction using poly I:C and the priming agent PMA. The Examiner cites *In re Kerkhoven* for the proposition that it is prima facie obvious to combine two compositions which are taught by the prior art to be useful for the same

purpose in order to form a third composition to be used for the very same purpose. The Examiner concludes it would have been obvious to combine the anti-apoptotic protein CrmA with the PKR cell line which are both allegedly capable of overexpressing cytokine products. The Examiner further relies on Suzuki et al. for allegedly suggesting the use of combining an apoptosis-suppressive gene including CrmA for the production of cytokines and Lau for allegedly teaching the PKR cell line can overexpress a cytokine. The Examiner further concludes one of skill in the art would be motivated to include CrmA in the PKR cell line because both can allegedly be used for the expression of proteins (cytokines) as allegedly taught by Lau and Suzuki et al.

Again, there must be some teaching or suggestion to combine references. The teaching of Lau is quite clear that production of cytokines is enhanced when cells are manipulated to express PKR, and nothing in the teaching suggests that cell life is too short to achieve this desired goal. Lau nowhere mention problems with cell apoptosis or shortened cell life. Thus, there is no motivation from the disclosure of Lau to modify the cell life according to the teachings of Dixit or Suzuki *et al.*

Contrary to the assertions of the Examiner, *In re Kerkhoven* is inappropriately applied in this case. The purpose of the CrmA gene and the purpose of the PKR gene in the art of record are different. For example, the purpose of the CrmA gene in the cited documents is to extend the life of the indicated cells. The purpose of the PKR gene in the cited documents is to overproduce desired cytokines. Therefore, *In re Kerkhoven* is inappropriately applied in this case. Accordingly, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. No such a showing has been made.

The requirement of "motivation" or "suggestion" to combine is a safeguard against the use of hindsight combinations. "[I]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that '[o]ne can not use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992) *citing In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). "It is impermissible ...simply to engage in a hindsight reconstruction of

the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps." *In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991). Applicant is aware that "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin* 170 USPQ 209, 212 (CCPA 1971). Here, the Examiner's judgment on obviousness necessarily includes knowledge gleaned from applicants' disclosure and is therefore improper.

Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

IV. Conclusion

It is respectfully submitted that each of the pending claims 1-3, 5-8, 11, 25, 26, 29, 31-34, 37, 39, and 40 are in condition for allowance. A Notice of Allowance is respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4308.

Respectfully submitted,

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